510(k) Summary

807.92 (a)(1): Name: Ventana Digital Pathology
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JUN - 1 2012

807.92 (a)(2): Device name- trade name and common name, and classification

Trade name: Virtuoso™ System for IHC p53(DO-7)

Common Name: Digital pathology and image analysis system for immunochemistry-stained slides

Classifications: 21 CFR § 864.1860- Immunohistochemistry reagents and kits

Product Codes: NOT, NQN, OEO

807.92 (a)(3): Identification of the legally marketed predicate devices

This Virtuoso System for IHC p53 (DO-7) is substantially equivalent to its immediate predecessor with the same name, cleared under K111872 on April 19, 2012. The two Virtuoso systems are identical, with the sole difference being the automatic stainer that can be used with the reagents to stain the glass slides. The first p53 submission qualified the Benchmark XT stainer, and this current submission qualified a second automatic stainer, the Benchmark ULTRA stainer.

807.92 (a)(4): Device Description

General Description

The Virtuoso™ System is an instrument-plus-software system designed to assist the qualified pathologist in the consistent assessment of protein expression in immunohistochemically stained histologic sections from formalin-fixed, paraffin-embedded normal and neoplastic tissues. The system consists of a slide scanner (iScan), computer, monitor, keyboard, mouse, image analysis algorithms for specific immunohistochemical markers, and software with a Windows web browser-based user interface. Virtuoso is a web-based, end-to-end, digital pathology software solution that allows pathology laboratories to acquire, manage, view, analyze, share, and report digital images of pathology specimens. Using the Virtuoso software, the pathologist can view digital images, add

annotations, make measurements, perform image analysis, and generate reports.

Hardware: The iScan slide scanning device captures digital images of formalin-fixed, paraffin-embedded tissues that are suitable for storage and viewing. The device includes a digital slide scanner, racks for loading glass slides, computer, scanner software, keyboard, mouse and monitor.

Software: The Virtuoso software is designed to complement the routine workflow of a qualified pathologist in the review of immunohistochemically stained histologic slides. It allows the user to select fields of view (FOVs) in the digital image for analysis and provides quantitative data on these FOVs to assist with interpretation. The software makes no independent interpretations of the data and requires competent human intervention for all steps in the analysis process.

Additional Materials Required:

- Ventana CONFIRM™ p53 (DO-7) rabbit monoclonal primary antibody
- Reagents for visualization, such as universal DAB chromogen
- Associated materials for completing immunohistochemical staining according to the appropriate package insert
- Color printer if user wishes to print color copies.

Device Quality Control

The quality of results depends on the laboratory following the quality control instructions recommended in the labeling of the immunohistochemistry (IHC) reagents. The software also performs a quality check on the digital images to determine if they are suitable for further analysis using "Image Quality Assessment" algorithms.

Summary of Procedure

Samples are obtained as formalin-fixed, paraffin-embedded tissue blocks. Histologic sections are prepared and mounted onto glass slides. Slides are reacted with the p53 (DO-7) primary antibody, and are then visualized using DAB. Prepared slides are loaded into the Virtuoso system scanner and scanned. The resulting digital images are reviewed by the pathologist on a computer monitor, and appropriate fields of view (FOVs) are then selected for analysis by the Virtuoso software. The Virtuoso software produces a quantitative score for the FOV and an aggregate score over all the FOVs for the whole slide. The pathologist has the choice of accepting the result or overriding with his/her own score for some or all FOVs.

807.92 (a)(5): Intended Use

The Virtuoso system provides automated digital slide creation, management, analysis, and viewing. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting, review and classification of tissues and cells of clinical interest based on particular morphology, color, intensity, size, pattern and shape.

The Virtuoso™ System for p53 (DO-7) is for digital read and image analysis applications. This particular Virtuoso system is intended for use as an aid to the pathologist in the detection and semi-quantitative measurement of p53 (DO-7) protein in formalin-fixed, paraffin-embedded normal and neoplastic tissue. This device is an accessory to the Ventana Medical Systems, Inc. CONFIRM™ anti-p53 (DO-7) Mouse Monoclonal Primary Antibody assay. The Ventana Medical Systems, Inc. CONFIRM™ anti-p53 assay is indicated for the assessment of p53 protein where mutations have been linked to tumor proliferation. When used with this assay, the Virtuoso™ System for p53 (DO-7) is indicated for use as an aid in the assessment of p53 status in breast cancer patients (but is not the sole basis for treatment).

Note: The IHC p53 (DO-7) Digital Read and Image Analysis applications are adjunctive computer-assisted methodologies for the qualified pathologist in the acquisition and measurement of images from microscope glass slides of breast cancer specimens stained for the presence of p53 protein. The pathologist should verify agreement with the Image Analysis software application score. The accuracy of the test results depends on the quality of the immunohistochemical staining. It is the responsibility of a qualified pathologist to employ appropriate morphological studies and controls as specified in the instructions for the CONFIRM™ anti-p53 (DO-7) Mouse Monoclonal Primary Antibody assay used to assure the validity of the Virtuoso System for IHC p53 Digital Read and Image Analysis scores. The actual correlation of CONFIRM™ anti-p53 (DO-7) Mouse Monoclonal Primary Antibody to clinical outcome has not been established.

807.92 (a)(6): Technological Similarities and Differences to the Predicate Devices

The following chart describes similarities and differences between the two test systems.

Characteristic	Virtuoso™ IHC p53 (DO-7) [Benchmark ULTRA Stainer]	Virtuoso™ IHC p53 (DO-7) [Benchmark XT Stainer] K111872
Intended Use/Indications for Use	This device is intended for in vitro diagnostic (IVD) use. The Virtuoso system provides automated digital slide creation, management, analysis, and viewing. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting, review and classification of tissues and cells of clinical interest based on particular morphology, color, intensity, size, pattern and shape. The Virtuoso™ System for p53 (DO-7) is for digital read and image analysis applications. This particular Virtuoso system is intended for use as an aid to the pathologist in the detection and semi-quantitative measurement of p53 (DO-7) protein in formalin-fixed, paraffin-embedded normal and neoplastic tissue. This device is an accessory to the Ventana Medical Systems, Inc. CONFIRM™ anti-p53 (DO-7) Mouse Monoclonal Primary Antibody assay. The Ventana Medical Systems, Inc. CONFIRM™ anti-p53 assay is indicated for the assessment of p53 protein where mutations have been linked to tumor proliferation. When used with this assay, the Virtuoso™ System for p53 (DO-7) is indicated for use as an aid in the assessment of p53 status in breast cancer patients (but is not the sole basis for treatment).	SAME SAME SAME
Specimen Type	Formalin-fixed, paraffin-embedded tissue stained by immunohistochemical technique	Same
System Operation (Digital Read and Image Analysis)	Histologic observation by a pathologist through the viewer and image analysis systems	Same
Hardware and Software	Ventana iScan slide scanner, computer, color monitor, proprietary software for p53 (DO-7))	Same
Platform Components	mouse, keyboard, windows web browser.	Same
Primary Antibody (Assay) Reagent	Ventana CONFIRM™ p53 (DO-7) (reagent is Class I, 510(k) exempt)	Same

Characteristic	Virtuoso™ IHC p53 (DO-7) [Benchmark ULTRA Stainer]	Virtuoso™ IHC p53 (DO-7) [Benchmark XT Stainer] K111872
Ancillary Reagents/Stainers	DAB universal chromogen kits, Slides stained with Benchmark ULTRA stainer	DAB universal chromogen kits, Slides stained with Benchmark XT stainer
Localization of IHC positive stain	Nucleus	Same
Interpretation	Interpretation is performed by the pathologist.	Same

807.92 (b)(1/2): Brief Description of Clinical Data (Non-clinical data N/A)

The Virtuoso System for IHC p53 (DO-7) with the Benchmark XT stainer was clinically validated via two studies. The first (primary) study evaluated overall system performance (concordance) across four sites in terms of agreement between the reference manual method (with a traditional microscope) and both the digital read (DR) and image analysis (IA) applications of the Virtuoso system. In the second study, system reproducibility was evaluated among three pathologists for inter-pathologist reproducibility of the two Virtuoso applications; also, intra-pathologist/inter-day reproducibility of the two Virtuoso applications was evaluated. The data from both studies are summarized below.

Agreement/Concordance

a. Virtuoso Digital Read vs Manual Method

Each pathologist's Virtuoso digital read results were compared to their manual results. The data were categorized as "neg" and "pos" using p53 classifications of less than or equal to 10% staining to describe negative, and greater than 10% to describe positive. The overall agreements across the four sites were: 93%, 95%, 94%, and 82%, respectively. The data, with the 95% confidence intervals (CI) around the agreements, and negative and positive agreements, are shown below.

Confusion Matrix		p53 (DO-7) Digital Read							
		Site 1 (n = 119)		Site 2 (n = 119)		Site 3 (n = 117)		Site 4 (n = 114)	
		Neg	Po	Neg	Po	Neg	Po	Neg	Po
Manual	Neg (≤10%)	73	0	82	6	71	4	56	20
	Pos (>10%)	8	38	0	31	3	39	1	37
	% Agreement	93%		95%		94%		82%	
	(95% CI)	(87% -	97%)	(89% -	98%)	(88% -	97%)	(73% -	88%)
Negative % Agreement		100%		93%		95%		74%	
(95% CI)		(95% -	100%)	(86% -	97%)	(87% -	98%)	(63% -	82%)
Positive % Agreement		83%		100%		93%		97%	
(95% CI)		(69% -	91%)	(89% -	100%)	(81% -	98%)	(87% -	100%)

b. Virtuoso Image Analysis vs Manual Method

The same analysis as performed for digital read was performed for image analysis. The overall agreements across the four sites were: 92%, 97%, 91% and 90%, respectively. That data table, along with the 95% CIs, and the negative and positive percent agreements, is presented below.

Confusion Matrix		P53 (DO-7) Image Analysis							
		Site 1 (n = 119)		Site 2 (n = 119)		Site 3 (n = 117)		Site 4 (n = 105)	
		Neg	Po	Neg	Po	Neg	Po	Neg	Po
Manual	Neg (≤10%)	72	1	84	4	71	4	61	6
	Pos (>10%)	9	37	0	31	7	35	4	34
	% Agreement	92%		97%		91%		90%	
	(95% CI)	(85% -	95%)	(92% -	99%)	(84% -	95%)	(83% -	95%)
Negative % Agreement		99%		95%		95%		91%	
(95% CI)		(93% -	100%)	(89% -	98%)	(87% -	98%)	(82% -	96%)
Positive % Agreement		80%		100%		83%		89%	
(95% CI)		(67% -	89%)	(89% -	100%)	(69% -	92%)	(76% -	96%)

Reproducibility

a. Intra-Pathologist/Inter-Day (pair-wise comparisons, Session 1 vs Session 2, Session 1 vs Session 3, Session 2 vs Session 3, using the 10% cutoff)

Digital Read

The agreements between each of three comparisons across three sessions with the same pathologist are shown below. The total agreements ranged from 90% to 95%, and the data (with 95% CIs) are shown below.

p53 Intra-Pathologist Digital- 10%									
Confusion Matrix			Session 2		Session 3		Session 3		
			Neg	Pos	Neg	Pos	Neg	Pos	
			26	14	25	15	25	15	
Session 1	Neg	27	26	1	25	2			
	Pos	13	0	13	0	13			
Session 2	Neg	26					24	2	
	Pos	14					1	13	
% Agreement			98%		95%		93%		
(95% CI)			(87% -	100%)	(83% -	99%)	(80% -	97%)	

Image Analysis

The agreements between each of the three comparisons across three sessions with the same pathologist are shown below. The agreements ranged from 80% to 93%, and the data (with 95% CIs) are shown below.

p53 Intra-Pathologist Image Analysis- 10%									
Confusion Matrix			Session 2		Session 3		Session 3		
			Neg	Pos	Neg	Pos	Neg	Pos	
			26	14	25	15	25	15	
Session 1	Neg	25	24	1	24	1			
	Pos	15	2	13	1	14			
Session 2	Neg	26					25	1	
	Pos	14					0	14	
% Agreement			93%		95%		98%		
(95% CI)			(80% -	97%)	(83% -	99%)	(87% -	100%)	

b. Inter-Pathologist/Site (pair-wise comparisons, Pathologist 1 vs Pathologist 2, Pathologist 1 vs Pathologist 3, Pathologist 2 vs Pathologist 3, using 10% cutoff)

Digital Read

The reproducibility in the Virtuoso digital readings among three pathologists/sites is shown below, along with the 95% CIs. The percent total agreements ranged from 94% to 99%.

Inter-Pathologist Digital p53 (DO-7)								
Confusion Matrix			Site 2		Site 3		Site 3	
			Neg	Po	Neg	Po	Neg	Po
			82	37	75	43	75	43
Site 1	Neg	81	81	0	74	6		
	Po	38	1	37	1	37		
Site 2	Neg	82					75	6
	Po	37					0	37
% Agreement			99%		94%		95%	
(95% CI)			(95% -	100%)	(88% -	97%)	(89% -	98%)

Image Analysis

The reproducibility in the Virtuoso image analysis interpretations among three pathologists is shown below, along with the 95% CIs. The percent agreements ranged from 94% to 97%.

Inter-Pathologist Image Analysis p53 (DO-7)								
Confusion Matrix			Site 2		Site 3		Site 3	
			Neg	Po	Neg	Po	Neg	Po
			84	35	79	39	79	39
Site 1	Neg	81	81	0	76	4		
	Po	38	3	35	3	35		
Site 2	Neg	84					79	4
	Po	35					0	35
% Agreement			97%		94%		97%	
(95% CI)			(93% -	99%)	(88% -	97%)	(92% -	99%)

PERFORMANCE with a SECONDARY STAINER (Benchmark ULTRA)

The Virtuoso System for IHC p53 (DO-7) with the Benchmark ULTRA stainer was clinically validated via a concordance study where 120 cases were evaluated three ways by one pathologist at one site. Each case was scored (1) manually with a routine microscope, (2) as a digital image, and (3) by way of the image analysis application. The manual score (reference result) was compared to both the digital read result and the image analysis result.

The data were evaluated as positive or negative for p53 status using up to 10% positive staining to define negative, and >10% to define positive. The data summaries follow, first for digital readings, and followed by image analyses.

Agreement: Digital Read vs Manual (manual = true score)
Negative= 0-10%; Positive= >10%

	Manual Microscopic Read		
Digital Read	**Positive**	**Negative**	**Total**
Positive	34	14	48
Negative	0	72	72
Total	34	86	120
Positive Percent Agreement (PPA) n/N (%) (95% CI)	34/34 (100.0) (89.8-100.0)		
Negative Percent Agreement (NPA) n/N (%) (95% CI)	72/86 (83.7) (74.5-90.0)		
Overall Percent Agreement (OPA) n/N (%) (95% CI)	106/120 (**88.3**) (81.4-92.9)		

Agreement: Image Analysis vs Manual (manual = true score)
Negative= 0-10%; Positive= >10%

	Manual Microscopic Read		
Image Analysis	**Positive**	**Negative**	**Total**
Positive	32	4	36
Negative	2	82	84
Total	34	86	120
Positive Percent Agreement (PPA) n/N (%) (95% CI)	32/34 (94.1) (80.9-98.4)		
Negative Percent Agreement (NPA) n/N (%) (95% CI)	82/86 (95.3) (88.6-98.2)		
Overall Percent Agreement (OPA) n/N (%) (95% CI)	114/120 (**95.0**) (89.5-97.7)		

807.92 (b)(3): Conclusions from Clinical Testing

Concordance studies and reproducibility studies were performed for the Virtuoso System for IHC p53 (DO-7) with the Benchmark XT stainer. Concordance studies were performed for the Virtuoso System for IHC p53 (DO-7) with a secondary stainer, the Benchmark ULTRA stainer. The test system was shown to be safe and effective for its intended use.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Ventana Medical Systems, Inc.
c/o Ms. Erika B. Ammirati, RAC, MT(ASCP)
Ammirati Regulatory Consulting
575 Shirlynn Court
Los Altos, CA 94022

JUN 0 1 2012

Re: k121350
Trade/Device Name: Virtuoso™ System for IHC p53 (DO-7)
Regulation Number: 21 CFR § 864.1860
Regulation Name: Immunohistochemistry reagents and kits
Regulatory Class: Class II
Product Code: NOT, NQN, OEO
Dated: May 3, 2012
Received: May 4, 2012

Dear Ms. Ammirati:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter

will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of *In Vitro* Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

INDICATIONS FOR USE

510(k) Number (if Known): K121350

Device Name: Virtuoso™ System for IHC p53 (DO-7)

Indications for Use

The Virtuoso system provides automated digital slide creation, management, analysis, and viewing. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting, review and classification of tissues and cells of clinical interest based on particular morphology, color, intensity, size, pattern and shape.

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Note: The IHC p53 (DO-7) Digital Read and Image Analysis applications are adjunctive computer-assisted methodologies for the qualified pathologist in the acquisition and measurement of images from microscope glass slides of breast cancer specimens stained for the presence of p53 protein. The pathologist should verify agreement with the Image Analysis software application score. The accuracy of the test results depends on the quality of the immunohistochemical staining. It is the responsibility of a qualified pathologist to employ appropriate morphological studies and controls as specified in the instructions for the CONFIRM™ anti-p53 (DO-7) Mouse Monoclonal Primary Antibody assay used to assure the validity of the Virtuoso System for IHC p53 Digital Read and Image Analysis scores. The actual correlation of CONFIRM™ anti-p53 (DO-7) Mouse Monoclonal Primary Antibody to clinical outcome has not been established.

Prescription Use __X__ AND/OR Over-The-Counter Use ____

(Part 21 CFR 801 Subpart D) (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostics (OIVD)

Division Sign-Off

Office of In Vitro Diagnostic
Device Evaluation and Safety

510(k) K121350